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(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway;

(c) forming a model drug response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of [an objective] a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said [objective] function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said [objective] function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

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42. (Amended) The computer system of claim 41 [where] wherein said steps of receiving comprise making said drug response [measurements] and said biological pathway [response measurements] responses available in said memory.

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44. (Amended) The computer system of claim 41 wherein said [objective] function comprises a sum of squares of the differences of said drug response and said model drug response at said levels of drug exposure, said model drug response being provided at said levels of drug exposure by transforming by said scaling transformations said levels of drug exposure to corresponding levels of perturbations to each of said biological pathways and by interpolating said biological pathway responses to said corresponding levels of perturbations.

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48. (Amended) The computer system of claim 41 wherein the method performed by said processor further comprises the steps of:

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- (f) determining an expected probability distribution of minimized determined values of said [objective] function, and
- (g) assessing the statistical significance of the minimized determined value of said [objective] function in view of the expected probability distribution of minimized determined values of said [objective] function.

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49. (Amended) The computer system of claim 48 wherein the expected probability distribution of minimized determined values of said [objective] function is determined by:

- (i) randomizing the drug response with respect to the plurality of levels of drug exposure and randomizing the model drug response by randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
- (ii) determining a theoretical minimum [values] value of the [objective] function of the difference between the randomized drug response and the randomized model drug response;
- (iii) minimizing said determined theoretical value of the [objective] function by varying the scaling transformations of the one or more randomized biological pathway responses to obtain scaling transformations that minimize said determined theoretical value of the [objective] function; and
- (iv) repeating steps (i) through (iii) to determine a plurality of theoretical minimum values,

wherein said plurality of minimum values forms said expected probability distribution of minimized values.

50. (Amended) The computer system of claim 41 wherein the method performed by the processor further comprises a step of verifying that said biological pathways are biological pathways involved in the action of said drug in said cell type by a method comprising selecting a model response that behaves most similarly to a combined drug-perturbation response, said combined drug perturbation response being provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of said cell type exposed simultaneously to one or more levels of said exposure to said drug and to one or more levels of perturbations in said one or more biological pathways,

wherein the model drug response is selected from the group consisting of:

- (i) a first model drug response comprising the combination of one or more biological pathway responses subject to the best scaling transformations evaluated at one or more first sums, each first sum being the sum of one of said one or more levels of drug exposure subject to said scaling transformations and one of said one or more levels of perturbations to said biological pathways.
- (ii) a second model drug response comprising one or more second sums, each second sum being the sum of said drug response evaluated at one of said one or more levels of drug exposure and said combination of said one or more biological pathway responses subject to the best scaling transformations evaluated at one of said one or more levels of perturbations to said biological pathways,

wherein said biological pathways are verified as biological pathways actually involved in the action of said drug in said cell type if the first model response is [selected] selected.

54. (Amended) The computer system of claim 41 wherein said one or more programs further cause said processor to interpolate the quantitative measurements of cellular constituents of the biological pathway in said cell of said cell type at a plurality of levels of perturbation so that the one or more biological pathway responses are interpolated.

61. (Amended) The computer system of claim 60 wherein the abundances of the plurality of RNA species are measured by a method comprising contacting a gene transcript array with RNA from a cell of the cell type, or with cDNA derived therefrom, wherein a gene [transcript] transcript array comprises a surface with attached nucleic acids or nucleic acid mimics, said nucleic acids or nucleic acid mimics being capable of hybridizing with said plurality of RNA species or with cDNA species derived therefrom.

62. (Amended) The computer system of claim 61 wherein the quantitative measurements of cellular constituents in step (a) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom,

from a cell of said cell type that is exposed to said drug, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said drug, and

wherein said quantitative measurements of cellular constituents in step (b) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is exposed to said perturbation to said biological pathway, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said perturbation to said biological pathway.

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69. (Amended) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllable transfection of genes [expression] expressing the one or more specific cellular constituents.

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74. (Amended) The computer system of claim 67 wherein the one or more specific cellular constituents are abundances of protein species or activities [or] of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the abundances in a cell of the cell type.

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76. (Amended) The [method] computer system of claim 74 wherein the method of controllably decreasing the abundances comprises exposing a cell of the cell type to antibodies, wherein the antibodies bind to the protein species.

77.(Amended) The [method] computer system of claim 67 wherein the one or more specific cellular constituents are activities of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the activities in a cell of the cell type.

78. (Amended) The [method] computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to drugs which directly and specifically inhibit the activities of the protein species.

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79. (Amended) The [method] computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to dominant negative mutant protein species, wherein the dominant negative mutant protein species are proteins inhibiting said activities.

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80. (Amended) A computer system for identifying a more pathway specific drug candidate [from] than an initial drug candidate comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) identifying the biological pathways involved in the action of an initial drug candidate by a method comprising:

- (i) receiving an initial drug response of said initial drug candidate in a cell of a cell type, said initial drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the initial drug candidate,
- (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway,
- (iii) forming a model initial drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
- (iv) determining the value of [an objective] a function of the difference between said initial drug response and said model initial drug response, and
- (v) minimizing the determined value of the [objective] function by varying the scaling transformation of said one or more biological pathways in

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the first combination to obtain a first set of best scaling transformations that minimize the determined value of the [objective] function, so that the combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the initial drug candidate;

(b) identifying the biological pathways involved in the action of a modified drug candidate, said modified drug candidate having a modified structure of the initial drug candidate, by a method comprising:

- (i) receiving a modified drug response of said modified drug candidate in a cell of the cell type, said modified drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the modified drug candidate,
- (ii) forming a model modified drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,
- (iii) determining the value of [an objective] a function of the difference between said modified drug response and said model modified drug response, and
- (iv) minimizing the determined value of the [objective] function of the difference between said modified drug response and said model modified drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the [objective] function,

so that the combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate, and

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wherein said modified drug candidate is identified as a more pathway-specific drug candidate than said initial drug candidate if fewer biological pathways are identified in the action of said modified drug candidate than in the action of said initial drug candidate.

81. (Amended) A computer system for identifying one or more specific biological pathways that are involved in the action of a drug and that mediate side-effects of the drug, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) identifying the biological pathways involved in the action of a first drug by a method comprising:
  - (i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the [first] first drug,
  - (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway,
  - (iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
  - (iv) determining the value of [an objective] a function of the difference between said first drug response and said model first drug response, and
  - (v) minimizing the determined value of the [objective] function by varying the scaling transformation of said one or more biological pathways in

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- the first combination to obtain a first set of best scaling transformations that minimize the determined value of the [objective] function, so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;
- (b) identifying the biological pathways involved in the action of a second drug by a method comprising:
- (i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,
  - (ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,
  - (iii) determining the value of [an objective] a function of the difference between said second drug response and said model second drug response, and
  - (iv) minimizing the determined value of the [objective] function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the [objective] function,
- so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate; and
- (c) identifying specific biological pathways involved in the action of the first drug that are different from those biological response pathways involved in the action of the second drug so that one or more specific biological pathways that



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are involved in the action of the first drug and that mediate side-effects of the first drug are identified.

82. (Amended) A computer system for identifying one or more specific biological pathways that are involved in mediating therapeutic efficacy for a disease or disorder, said computer system comprising:  
a processor, and  
a memory coupled to said processor and encoding one or more programs,  
wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) identifying the biological pathways involved in the action of a first drug by a method comprising:
  - (i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,
  - (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway,
  - (iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
  - (iv) determining the value of [an objective] a function of the difference between said first drug response and said model first drug response, and
  - (v) minimizing the determined value of the [objective] function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the [objective] function,

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so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

- (b) identifying the biological pathways involved in the action of a second drug by a method comprising:
- (i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,
  - (ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,
  - (iii) determining the value of [an objective] a function of the difference between said second drug response and said model second drug response, and
  - (iv) minimizing the determined value of the [objective] function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the [objective] function,
- so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate; and
- (c) identifying specific biological pathways involved in the action of both the first and second drugs so that one or more specific biological pathways that are involved in the action of said first drug and mediate therapeutic efficacy for the disease or disorder are identified.

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83. (Amended) A computer system for identifying biological pathways involved in the action of a drug in a cell type comprising a process, and a memory coupled to said processor and encoding one or more programs, wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of [an objective] a function of the difference between a provided drug response and a model drug response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways;
- (b) said provided drug response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said drug; and
- (c) said model drug response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations identifies the biological pathways involved in the action of said drug in said cell type.

84. (Amended) The computer system of claim 83 wherein said computer system assigns a statistical significance to the combination of said one or more biological pathway responses subject to said best scaling transformations, wherein the statistical significance is assigned by a method comprising:

- (a) obtaining an expected probability distribution of minimized values of the [objective] function; and
- (b) assessing statistical significance of an actual minimized value of the [objective] function in view of the expected probability distribution, wherein

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the actual minimized value of the [objective] function is determined from the provided drug response and the model drug response.

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- (a) randomizing the drug response with respect to the plurality of levels of drug exposure, [;
- (b)] or, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
- [(c)]
- (b) determining a theoretical minimum value of the [objective] function by determining best scaling transformations of the one or more randomized biological pathway responses which minimize [an objective] the function of the difference between the [randomized] drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or a theoretical minimum value of the function by determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized;
- and
- [(d)]
- (c) repeating steps (a) through [(c)] (b), so that a plurality of theoretical minimum values is thereby determined,

wherein the plurality of theoretical minimum values forms the expected probability distribution.

86. (Amended) A computer system for identifying biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:  
a processor, and  
a memory coupled to said processor and encoding one or more programs,  
a memory coupled to said processor and encoding one or more programs,

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wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of an objective function of the difference between a received environmental response and a model environmental response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways;
- (b) said received environmental response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said environmental change; and
- (c) said model environmental response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations identifies the biological pathways involved in the effect of said environmental change upon said cell type.

87. (Amended) A computer system for identifying biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) receiving an environmental response to said environmental change upon said cell type, said environmental response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of exposure to said environmental change;
- (b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of